Summary Basis for Regulatory Action

Date: August 24, 2009
From: Michael Kennedy, Chair of the Review Committee <ESIG>
BLA/ STN#: STN 125329/0
Applicant Name: Bio Products Laboratories
Date of Submission: November 18, 2008
PDUFA Goal Date: September 17, 2009
Proprietary Name/ Established Name: Gammaplex®/ Immune Globulin Intravenous (Human), 5%
Indication: Treatment of Primary Immune Deficiency patients
Recommended Action: Approval

Signatory Authorities Action:
Offices Signatory Authority: Ginette Michaud M.D.,_____

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Offices Signatory Authority: Mary Malarkey,_____

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Specific documentation used in developing the SBRA Reviewer Name – Document(s) Date
Clinical Review: Hon Sum Ko/ Nisha Jain (Pediatrics)
Clinical Pharmacology Review: Iftekhar Mahmood
Statistical Review; Xue Lin
CMC Review: M. Kennedy/M. Mikolajczyk/D. Frazier [Viral Safety] Lilin Zhong/ Pei Zhang
Pharmacology/ Toxicology Review: Evi Struble
Biomonitoring Review: Anthony Hawkins
Facilities (DMPQ) James Crim/ Randa Melhem
Labeling (APLB) Liza Stockbridge
Pharmacovigilance: Ann Gaines/ Craig Zinderman
RPM : Debbie Cordaro

1. Introduction

Bio Products Laboratory (BPL) Immune Globulin Intravenous (Human), Gammaplex® is a 5% solution of human normal immunoglobulin G (IgG) from healthy US plasma donors. This IGIV product is a modification of the BPL's current IGIV product Vigam® Liquid which is licensed in the UK and has been marketed there since 1997. Gammaplex differs from Vigam Liquid by the addition of a 20 nm viral filtration step in the manufacturing process, and changes in its formulation. Unlike Vigam, Gammaplex does not contain sucrose and albumin in its formulation; three excipients are added for stability and to prevent aggregation; sorbitol, glycine, and polysorbate 80. Due to these manufacturing and formulation changes, Gammaplex is considered a new product. Gammaplex is manufactured using -------(b)(4)--------- fractionation to the ----------(b)(4)----------, followed by solvent/detergent incubation, ------(b)(4)------ ion-exchange chromatography, 20 nm nano-filtration, -(b)(4)-, final formulation to bulk drug substance, sterile filtration, final-product filling, with a terminal high temperature/low pH hold ---------(b)(4)---------- product (----------(b)(4)----------). There are no unusual processing steps in the Gammaplex manufacturing process and BPL has been using only United States source plasma in its manufacturing facility since 1998. BPL performed formulation studies during the development of Gammaplex and the stability studies necessary to support the choices made for the Gammaplex formulation. The final formulation is: --(b)(4)--% protein consisting of ≥ 95% IgG, -(b)(4)- mM sodium chloride, -(b)(4)- mM glycine, -(b)(4)- mM sorbitol, -(b)(4)- µg/mL polysorbate 80, pH 4.8 – -(b)(4)-. Gammaplex is filled at 50 ml, 100 ml, and 200 ml sizes (2.5 g, 5 g, and 10 g) in Type II glass bottles.

2. Background

The Biologics License Application (BLA) from Bio Products Laboratories (Elstree, UK) for was received by CBER on November 17, 2008 requesting U.S.-licensure of a 5% Liquid Immune Globulin Intravenous (Human) product, trade name Gammaplex and received a standard 10 month BLA review schedule. The clinical studies were conducted under BB-IND --(b)(4)-- for the indication of primary humoral immunodeficiency (PID), and a pre-BLA meeting was held on 2/20/08. In the current BLA submission, the treatment of patients with PID is the only indication being sought. The BLA contains data from one phase 3 trial to determine safety, efficacy, and pharmacokinetics of Gammaplex in PID patients. An additional clinical study was performed to compare the pharmacokinetics, safety, and tolerance, of BPL's two liquid IVIG products (Vigam Liquid and Gammaplex) in healthy adult volunteers. The application submitted for Gammaplex was very complete and required relatively few information requests. A DMPQ-led preapproval inspection was performed in May 2009 with the general consensus among the inspectors that the facility was at a high level of compliance and only a few issues being raised during the course of the inspection. While Gammaplex is the first BPL product to be submitted for a US license, BPL is an experienced manufacturer which has experience in the regulated environment in the United Kingdom. Although the regulatory framework of the MHRA is not identical to US regulations it does have many similarities and the Company's management seemed knowledgeable

about current US regulations. BPL is a not-for-profit organization, wholly owned by the British Government. Its research, development, manufacturing and UK and overseas marketing departments are all based at Elstree, Hertfordshire, UK. The Elstree site has been a medical research facility for more than 100 years and blood products have been manufactured there for more than 50 years. BPL, in its current configuration, has operated a blood products manufacturing facility there for almost 20 years. The legal status of BPL in the United Kingdom is Under the Secretary of State for Health in the Department of Health which is regulated in the UK by the MHRA. The MHRA performs inspectional and licensing duties on BPL. The last inspection of BPL by the MHRA occurred in 2008.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Source Plasma: BPL obtains US source plasma from licensed centers operated by ----------(b)(4)----------. The plasma is screened and tested for antibodies to HCV and HIV, including HBsAg, followed by minipool testing by NAT/PCR for HIV, HBV, HCV, HAV and Parvovirus B19. Plasma supplied to BPL is frozen, stored, and transported, under appropriately validated processes. Prior to fractionation, source plasma is stored at BPL for ----(b)(4)----- at a temperatures not exceeding -20°C. Manufacturing plasma pools are tested for anti-HIV1 and 2 antibodies, HBsAg, HCV RNA and parvovirus B19 DNA. The parvovirus B19 DNA limit for the manufacturing plasma pools is set as $\leq 10^4$ IU/mL. All other raw materials used in the manufacture of Gammaplex are obtained from appropriately qualified vendors, quarantined on receipt, tested by validated methods, and released to manufacturing by QA personnel.

Manufacturing process:

[-----(b)(4)-----]

[-----(b)(4)-----]

Specifications: Specifications and validation of analytical methods have been evaluated by review personnel and discussed with the firm during the Pre-Approval Inspection. The final specifications and acceptance limits established for Gammaplex by BPL are within the ranges seen for other IGIV products and were determined to be acceptable. The specifications are established based on the results of conformance batches, historical product data from BPL's other IGIV products, and the outcome of clinical studies. The testing program for Gammaplex includes appropriate measures of product quality attributes, product impurities, and parameters known to effect IGIV safety. All routine methods used as control or release testing of starting materials, process intermediates, drug product, and stability samples, were validated and appropriate implemented.

	Test	Limits		
		2.5 g	5.0 g	10 g
Characteristics	Appearance of solution	Complies		
	pH at 20°C	4.8 – (b)(4)		
	Osmolality, mOsmol/kg	(b)(4)		
Biological Safety Tests	Sterility	Pass		
	Pyrogenicity °C/n rabbits	Pass		
	Endotoxin (b)(4) EU/mL	(b)(4)		
	General Safety Test	Pass		
Viral Marker Tests	Hepatitis Bs Antigen	(b)(4)		
	Anti-HIV (1 and 2)			
Purity/Specific Function	Anti-HBsAg, IU g/IgG			
	Anti-HAV, IU g IgG			
	Anti-Parvovirus B19, IU/mg IgG			
	(b)(4)			
	Total protein, g/L			
	Protein Composition, gammaglobulin, %	≥ 95		
	(b)(4)	(b)(4)		
	Anti-diphtheria			
	Anti-measles			
	Anti-poliovirus			
Excipients	Sodium, mM			
	Chloride, mM			
	Glycine, mM			
	Acetate, mM			
	Sorbitol, g/L			
	Polysorbate 80, µg/mL			
Contaminants	Anti-A, Anti-B Haem-agglutinins (b)(4)			
	Anti-D			
	IgA (b)(4)			
	(b)(4)			

Stability of IGIV Final Drug Product

The stability-study data provided in the BLA was deemed sufficient to support the proposed storage conditions for final-product Gammaplex of 24 months at 2 °C to 25 °C. The following graphs display the primary aspects of Gammaplex stability at 25 °C over the course of the 24 month dating period.

[-----(b)(4)-----]

Control of Adventitious Agents

Gammaplex is manufactured only from US source plasma. The plasma is screened and tested for antibodies to HCV and HIV, including HBsAg, followed by minipool testing by NAT/PCR for HIV, HBV, HCV, HAV and Parvovirus B19. The Gammaplex process contains three manufacturing steps which contribute to viral inactivation or removal - solvent/detergent virus inactivation, 20nm filtration step, and a terminal incubation at high temperature/low pH. These step are robust and validated to yield the following levels of viral inactivation or removal:

	Log_{10} Reduction			
Process step	**Solvent Detergent**	**20nm Filtration**	**Terminal Low pH / -(b)(4)- Incubation**	**Total LRV**
HIV 1	>6.8	I	>6.1	>12.9
SIN	>6.7	6.2	>7.3	>20.6
WNV	>6.4	I	NT	>6.4
BVDV	>5.6	I	>6.1	>11.7
IBR	≥5.0	I	>6.3	>11.3
HAV	NA	>4.8	1.1	>5.9
EMC	NA	>4.8	2.7	>7.5

HIV:	Human immunodeficiency virus
SIN:	Sindbis virus, model for hepatitis C virus (HCV)
WNV:	West Nile Virus
BVDV:	Bovine viral diarrhea virus, model for HCV
IBR:	Infectious bovine rhinotracheitis, bovine herpesvirus model for enveloped DNA viruses including hepatitis B
HAV:	Hepatitis A virus
EMC:	Encephalomyocarditis, model for HAV
NA:	Not applicable, solvent detergent step is limited to the inactivation of enveloped viruses
I:	Inactivation by the product intermediate precluded the accurate estimation of the removal of these viruses by the filtration step
NT:	Not tested

----------(b)(4)----------

Conclusion

The CMC reviewers (M. Kennedy, M. Mikolajcyzk, D. Frazier, P. Zhang, L. Zhong) find that sufficient data and information has been provided on the chemistry, manufacturing, and controls to support licensure of BPL's IGIV.

b) CBER Lot Release - Confirmatory testing at CBER is not suggested at this time. Mode of Lot Release: The product is an IGIV, similar to many other licensed IGIV products for which CBER does not perform routine lot release testing. Lot release tests performed by the manufacturer BPL (Bio Products Laboratory) are appropriate to assure the safety and potency of this product and include Sterility, Pyrogenicity, General Safety, ---(b)(4)--- EU/mL), ----------(b)(4)----------, Anti-A and B Hemagglutinins, Anti-Rho(D), Purity (Protein Comp. IgG), Identity, Antibody Integrity (-(b)(4)-). The results of these tests are reviewed upon submission of the Lot Release Protocol for each lot manufactured. This is BPL's first biologic product for US release; however, BPL has manufactured IGIV products for the UK market for many years. The pre-licensing inspection findings and BLA submission review show that all of the release tests are appropriately performed and validated. Confirmatory testing at CBER was not suggested by the product reviewers for Gammaplex.

The following forms the rationale for the testing plan:

Safety and Purity –

1. Tests for safety and purity performed by BPL and reviewed by CBER include Sterility, Pyrogencity, General Safety, --(b)(4)-- EU/mL), ----------(b)(4)----------, and Anti-A and B Hemaggultinins, and anti-Rho(D).

2. Gammaplex is produced only from US plasma collected at licensed US blood collection centers. All plasma donations are screened for viral markers including anti-HIV 1 and 2 antibodies, HBsAg, and anti-HCV antibodies. Plasma is also tested by NGI NAT for HIV, HAV, HBV, HCV and parvovirus B19. The parvovirus B19 DNA limit for the manufacturing plasma pools is set as less than or equal to 10^4 IU/mL.
3. Bio Product Laboratories has used only US sourced plasma in all its manufacturing operations since 1998.
4. The manufacturing process for Gammaplex contains no unusual or unique manufacturing steps.
5. The manufacturing process for Gammaplex contains a number of robust viral clearance/ viral inactivation manufacturing steps.
6. Cold ethanol fractionation of human plasma is a widely used manufacturing process with a long history of producing high quality pharmaceutical products.

Potency and Identity –

1. Tests for potency and identity performed by BPL and reviewed by CBER include Purity (Protein Comp. IgG), Identity and Antibody Integrity (--(b)(4)--).
2. BPL has submitted in the BLA clinical trial results from well designed and appropriately executed clinical studies which support the efficacy of this product.

c) Facilities review/inspection

There is a single site for manufacturing:

Bio Products Laboratory
Dagger Lane, Elstree
Hertfordshire, United Kingdom
The FEI number is 1000184635.

The DMPQ led pre-approval inspection took place on May 15-22, 2009. The scope of this inspection was to evaluate the quality and manufacturing operations for the product. The manufacturing processes for Immunoglobulin performed at the Hertfordshire building (-(b)(4)-) site include plasma fractionation, chromatography, nano-filtration, formulation, as well as the fill, finish, inspection and labeling of the final product. Analytical testing performed includes start pool virology testing, release and stability testing of the drug product. All on site testing takes place within the QC laboratories which are housed in Building -(b)(4)-. At the conclusion of the inspection, a three item list of inspectional observations, was issued to and discussed with management. The inspectional observations are summarized as follows:

1. Incomplete microbial ingress studies used to test the container closure integrity on the final product container.
2. Process Validation studies are not completed.
3. Master Production records and control records did not include complete manufacturing and control instructions.

BPL promptly responded to the 483 items and the company responses were found to be acceptable by the inspectors.

d) Environmental Assessment
On August 21, 2009 DMPQ reviewer James Crim filed a memo recommending that BPL be granted a categorical exclusion under 21 CFR 25.31 (c) with the concurrence of the DMPQ Division Director.

4. Nonclinical Pharmacology/Toxicology

Toxicology: Polyclonal immune globulin preparations of human origin, such as Gammaplex, have long been used in the clinic as replacement therapy in patients with humoral immunodeficiencies. Based on the clinical experience of such products, and the excipients for this product, limited preclinical toxicity testing was needed to support its licensure for Gammaplex. BPL submitted one toxicology study performed according to Good Laboratory Practices (21 CFR 58) that examined the hemodynamic effect of intravenous administration of Gammaplex in rats. In this study, a total of 24 male --(b)(4)-- rats or 8 rats per group, received a dose of 630 mg/kg of either Vigam Liquid, or Gammaplex or Gammaplex vehicle control, via a femoral vein catheter. The pressure and heart rate were recorded using a carotid artery catheter. Gammaplex caused no significant cardiovascular effects in rats at an infusion rate of 4.2 mL/kg/h. This rate is approximately the same as the maximal infusion rate of 4.8 mL/kg/h proposed for Gammaplex. A mild to moderate rise in blood pressure (20% maximum increase) was observed during and after an infusion of Gammaplex at the infusion rates in excess of 6 mL/kg/h. The occurrence of such hypertensive responses in rats could be related to the osmotic load on the vasculature which depends on the rate of infusion.
The formulation and excipients used in Gammaplex are present in other licensed IV products and considered safe.
In conclusion, based on the nonclinical data presented, the safety profile of Gammaplex when used at doses and infusion rates proposed presented no preclinical concerns.

5. Clinical Pharmacology

Protocol GMX01. A Phase III, Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex in Primary Immunodeficiency Diseases

In a multicenter, open-label, non-randomized study of PID patients, fifty subjects were enrolled in order to obtain 40 evaluable subjects. Twenty-four subjects participated in the pharmacokinetic (PK) sub-study. There were 9 subjects on the 21-day infusion schedule, and 15 subjects were on the 28-day infusion schedule. Gammaplex was infused (300 to 800 mg/kg/infusion every 21 or 28 days) by an infusion pump and the maximum rate for an infusion was 0.08 mL/kg/min. Blood samples for PK analysis of total IgG were obtained after infusion 7 for subjects on a 28-day schedule and after infusion 9 for subjects on a 21-day schedule. At infusion 7 or infusion 9, blood samples were obtained just before the infusion, immediately at the end of the infusion, 1 hour after the end of the infusion, 24 hours, and on days 2, 4, 7, 14, 21, and 28 after the start of the infusion. Non-compartmental analysis was used to estimate the PK parameters of total IgG and specific antibodies.

Total exposure, as measured by $AUC_{(0\text{-}tau)}$ was slightly greater for the 28-day infusion schedule than 21-day infusion schedule. The mean half-life was 41.1 ± 19.2 days for all 24 subjects (41.6 ± 26.5 days for the 21-day infusion schedule, and 40.8 ± 13.8 days for the 28-day infusion schedule).

Pharmacokinetic parameters of total IgG in patients with PID (mean ± sd)

Parameter (unit)	**21-day Dosing Interval (n=9)**	**28-day Dosing Interval (n=15)**
	Mean ±SD (Range)	Mean ± SD (Range)
C_{max} (mg/mL)	21.6 ± 3.8 (16.3-27.3)	21.4 ± 4.3 (15.9-31.0)
T_{max} (hr)	5.4 ± 7.2 (2.1-24.5)	6.1 ± 11.6 (2.4-48.1)
$AUC_{0\text{-}tau}$ (days*mg/mL)	289 ± 41 (214-365)	346 ± 52[a] (262-455)[a]
Half-Life (days)	42 ±26 (22-108)	41 ±14[a] (22-70)[a]
Clearance (mL/days/kg)	0.59 ±0.24 (0.19-1.02)	0.58 ±0.27[a] (0.24-1.28)[a]

Study GMX03. A comparison of the pharmacokinetics, safety and tolerance of two formulations of a liquid IVIg (Vigam Liquid and Gammaplex) using standard and accelerated infusion rates in healthy adult volunteers (three treatment arms) [Initiated 8/25/04, completed 12/23/04]. The treatment groups were as follows: Group 1 – 12 subjects receiving a single dose of Vigarn Liquid at 400 mg/kg intravenously, infused at an initial rate of 0.01 ml/kg/min increasing to a maximum of 3 mL/min; Group 2 – 12 subjects receiving a single dose of Gammaplex at 400 mg/kg intravenously infused at an initial rate of 0.01 mL/kg/min increasing to a maximum of 3 mL/min; Group 3 – 12 subjects receiving a single dose of Gammaplex at 400 mg/kg intravenously infused at an initial rate of 0.01 mL/kg/min increasing to a maximum of 6 mL/min. All 36 subjects had measurable increments of IgG over baseline up to at least Day 22. Although demonstrating wide inter-subject variability, serum concentrations of IgG were similar in terms of mean data in all three treatment groups over time except at 15 minutes post-dose when mean incremental serum levels of IgG were marginally lower in the Vigam Liquid treated group (8.0 g/L, 9.4 g/L and 9.8 g/L in Groups 1, 2 and 3, respectively). This was not considered clinically significant. From Day 3 onwards, mean incremental serum concentrations were almost identical in all three treatment groups. By Day 71, serum levels of IgG were less than 1 g/L over baseline in all three treatment groups. With the exception of Cmax, where the lower confidence interval fell just above 100%, all PK variables used to compare Vigam Liquid and BPL IGIV (with Vigam Liquid as the reference) infused up to 3 mL/min (Group 2 versus Group 1), showed confidence intervals which straddled 100% with point estimates within approximately 10% of 100, suggesting comparable bioavailability between products. The intervals did however fall marginally outside the 80-125% window required to absolutely confirm bioequivalence. The wide confidence interval observed can be attributed to wide inter-subject variability in serum IgG. The difference in Cmax is not considered clinically relevant.

The results for the comparison of Vigam Liquid and BPL IGIV infused up to 6 mL/min (Group 3 versus Group 1) also confirmed similar bioavailability. For this comparison, AUC0-21 data demonstrated bioequivalence with a confidence interval within the accepted range.

Pharmacokinetic parameters of IgG in 3 groups of healthy subjects (mean ± sd)

Parameters	Group 1	Group 2	Group 3
C_{max} (mg/mL)	8.3 ± 1.5	9.4 ± 1.2	9.8 ± 1.2
$AUC_{(0-\infty)}$ days*mg/mL	194 ± 69	181 ± 55	171 ± 59
CL (mL/day/kg)	2.9 ± 2.9	2.4 ± 1.2	2.6 ± 1.0
Half-life (hrs)	26 ± 9	22 ± 6	22 ± 8

Conclusions

The clinical pharmacology reviewer (Iftekhar Mahmood) considers this submission approvable on the basis of the pharmacokinetics information provided.

6. Clinical/ Statistical

a) Clinical Program

BPL submitted the following clinical data in support of Gammaplex for the indication of primary humoral immunodeficiency (PID). A single Phase III safety and efficacy study in patients with PID (GMX01) and a single PK/safety study in healthy volunteers (GMX03) were submitted in this application. The Phase III clinical trial GMX01, studied the efficacy of Gammaplex as replacement therapy in patients with PID. It was an open-label, uncontrolled study in 8 U.S. centers, with 50 subjects receiving Gammaplex 300 to 800 mg/kg at 3 or 4 week intervals for 12 months. Samples from a 24 subject subset of the study participants were also analyzed for pharmacokinetics.

The PK and safety study GMX03 compared the pharmacokinetics (PK) of Gammaplex with Vigam, another BPL IGIV product which is not marketed in the United States. It enrolled 36 healthy volunteers dosed with either product at 400 mg/kg (12 subjects/ group), with infusion rates up to 3 mL/min, and for Gammaplex, also up to 6 mL/min in a third group of 12 subjects. No safety concerns were observed in the healthy volunteers studied.

Efficacy

BPL studied Gammaplex under BB-IND --(b)(4)-- for the indication of primary humoral immunodeficiency, and a pre-BLA meeting was held on 2/20/08. The GMX01 study was the single human efficacy study was submitted to support the application:

Protocol GMX01. A Phase III, Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex in Primary Immunodeficiency Diseases

STUDY DESIGN: Phase 3, multicenter, non-randomized, open-label study to be conducted at 10 sites in the US, with a minimum of 50 subjects to be enrolled to give $\geq$40 evaluable subjects, and $\geq$20 subjects to give blood for pharmacokinetics (PK) of BPL IGIV: $\geq$7 of them on 21-day infusion cycles and $\geq$13 on 28-day cycles. Two batches of BPL IGIV, VSCN6845 (expiration date of 09 December 2006) and VSCN7045

(expiration date of 20 September 2007), were used in this study. In designing the protocol for this study, the following guidelines were followed:

- US Food and Drug Administration: *Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*
- Committee for Proprietary Medicinal Products: *Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IGIV)*

STUDY OBJECTIVES:
Primary: to determine if BPL IGIV was efficacious with respect to the FDA's minimal requirement of no more than 1 serious, acute, bacterial infection per subject per year in subjects with PID. Serious, acute infections were defined as outlined in FDA's guidance: *Safety, Efficacy and Pharmacokinetic Studies to Support Marketing of Immune Globulin Intravenous (Human) as Replacement Therapy for Primary Humoral Immunodeficiency*

Secondary: To assess the safety and tolerability of BPL IGIV. To determine if BPL IGIV has a PK profile comparable with that of intact IgG in subjects with PID

The effectiveness of Gammaplex was demonstrated in GMX01 by the absence of acute serious bacterial infections during the one-year treatment period with either 21- or 28-day treatment regimens. The patients were between 9 to 78 years of age, with 46 of them having common variable immunodeficiency (92%) and the remainder having X-linked agammaglobulinemia (8%). There were 26 males (52%) and 24 females (48%). Forty-six (92%) of patients were Caucasian. The primary efficacy endpoint was the development of serious acute bacterial infections over a 12-month observation period (99% confidence interval upper bound of one serious acute bacterial infection per subject per year).

Efficacy Conclusions: Gammaplex has met the primary and secondary efficacy endpoints and objectives set for it in this study, as (1) infusion of BPL IGIV into subjects with PID prevented the development of serious, acute, bacterial infections over the duration of this study, (2) infections that did occur could usually be managed with medical intervention at the physician's office and therapeutic use of systemic antibiotics, and (3) PK results of BPL IGIV were consistent with the intravenous administration of an intact human IgG product.

Statistical Analysis
Efficacy: The submission included one Phase 3, single- arm, open-label, multi-center study. The objective of the study was to evaluate the efficacy, safety, and pharmacokinetics of Gammaplex. The primary efficacy endpoint was the serious, acute, bacterial infection rate. The one-sided 99% upper confidence limit for the rate needs to be less than 1 to meet the FDA's efficacy requirement.

Safety: An important safety endpoint is the proportion of infusions with 1 or more temporally associated Adverse Events (AEs). To meet the FDA's safety requirement, the one-sided 95% upper confidence limit for the proportion needs to be less than 40%.
The study enrolled 50 subjects all of which had at least one infusion of the study drug.

The sponsor reported that of the 703 infusions, 149(21.2%) are associated with at least one AE up to 72 hours after the infusion. The one-sided 95% upper confidence limit for the proportion is 23.9%, which is less than FDA's safety threshold value 40%. The results are confirmed by the statistical reviewer. For some AEs, the information on the time relative to infusion was missing, so a worst case analysis was conducted; all AEs happened on the same day of an infusion or within 4 days after the infusion are included in the analysis. This sensitivity analysis shows that the proportion of infusions with an AE is 25.7%. The corresponding one-sided 95% upper confidence limit is 28.6% (< 40%).

Statistical Conclusions:
The study results show that Gammaplex meets both FDA's efficacy and safety recommendations listed above. No serious, acute, bacterial infection was observed during the study period. With zero mean infection rate per subject year, the one-sided 99% upper confidence limit was 0.101 per subject year using the exact method implemented in --(b)(4)-, which is less than FDA's efficacy threshold value of 1. The one-sided 95% upper confidence limit for the proportion of infusions with at least one AE up to 72 hours after the infusion is 23.9%, which is less than FDA's safety threshold value of 40%. Based on all the necessary statistical evaluations, the statistical reviewer has no objection to the licensure of this product.

Bioresearch Monitoring (BIMO) summary of Clinical Site Inspections
BACKGROUND
There were four clinical investigator site inspections performed in support of this Biologics License Application (BLA). Study subject population, geographic distribution and field resource considerations were among the factors used to select the inspected sites. Information from the BLA was compared to source documents, during the inspections. Clinical Investigator Sites:

	Site #	#Subjects	483	Inspection Classification
Buffalo, New York	001	5	Yes	VAI
Chicago, Illinois	005	12	Yes	VAI
Seattle, Washington	006	7	Yes	VAI
Irving, Texas	010	7	Yes	VAI

Study Title:
A Phase III, Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex in Primary Immunodeficiency Diseases
(Protocol GMX01)

NOTEWORTHY INSPECTIONAL FINDINGS
There were a few minor problems noted. The clinical investigator administered Gammaplex to five subjects on more than 20 occasions using a 180 micron filter instead of the protocol required 15-20 micron filter; the site discontinued the 180 micron filter after receipt of a sponsor notification regarding acceptable product administration sets including proper filter size, four months after the initial treatment of subjects. (Site 001)

Six subjects received a total of more than two dozen Gammaplex infusions without using any administration filter including the protocol-required 15 to 20 micron filter. (Site 010) Five subjects received 39 total infusions of Gammaplex at dosage levels that were different from the same dosage used previously to establish steady state, as required by the protocol. The clinical investigator did not report one serious adverse event (uterine bleeding and hospitalization) to the sponsor or the IRB, as required by the protocol (Site 005). More than a dozen Gammaplex infusions took place later than the protocol-specified start time limit (range: 15 minutes to 1 hour 20 minutes late). Subject vital signs were not always obtained using the same body position, as required by the protocol (Site 006). The clinical investigator enrolled three subjects who did not meet all the inclusion and exclusion criteria including time interval for prior receipt of licensed or investigational IGIV replacement therapy. There were study drug accountability discrepancies including Gammaplex receipt, destruction and dispensing for treatment of subjects; the study monitor noted no such accountability discrepancies (Site 010).

b) Pediatrics

The Pediatrics Review Committee waived and deferred the following PREA (under 21 U.S.C. 355c) requirements for Gammaplex:

- The pediatric study requirement for ages [0] to [<2] years was waived because the necessary studies are impossible or highly impracticable. It is rare for primary humoral immunodeficiency to be diagnosed in this age group.

- The submission of BPL's pediatric study for ages [≥2] to [16] years was deferred for this application because this product is ready for approval for use in adults and the pediatric study has not been initiated. Please see the post-marketing requirement that was put in place for this pediatric study in section 11 (d).

c. Other Special Populations
No other special populations are under consideration for the use of this IGIV product.

d. Overall Comparability Assessment
The review committee has determined that Gammaplex has comparable product efficacy, safety profile, manufacturing quality, product stability, product specifications, and product purity, to other IGIV's currently being marketed for the treatment of PID.

7. Safety

Two human safety studies are submitted in the BLA to support the safety of Gammaplex:
- Protocol GMX01. A Phase III, Multicenter, Open-Label Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Gammaplex in Primary Immunodeficiency Diseases
- Study GMX03. A comparison of the pharmacokinetics, safety and tolerance of two formulations of a liquid IVIg (Vigam Liquid and Gammaplex) using standard and accelerated infusion rates in healthy adult volunteers (three treatment arms)

Safety Parameters:
Laboratory parameters (routine hematology, biochemistry, urinalysis and immunology) were collected, together with physical examination, 12 lead electrocardiogram (ECG), vital signs and adverse events (AEs). A venous blood sample was also tested for various viral markers (anti-HIV 1 and 2, anti-HCV and HBsAg) at screening, immediately before dosing and at the final visit.

a) Adverse Events
    - Number and percent of infusions associated with AEs that began during the infusion or within 48 hours and 72 hours after completion of the infusion were calculated.
    - Nature, severity, and frequency of AEs (tolerability)
    - SAEs
    - Suspected unexpected serious adverse reactions (SUSARs), if any
b) Vital signs
c) Physical examination
d) Clinical laboratory tests, Direct Coombs' Test and Testing for Transmission of viruses
e) Urinalysis with microscopic examination at the central laboratory.

The following clinical laboratory tests were done by a central laboratory:

- Laboratory A. Alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), bilirubin, creatinine, blood urea nitrogen (BUN), and a complete blood count (CBC) with differential
- Laboratory B. The presence of Parvovirus B19, HCV, and HIV was determined with PCR (NAT). The presence of HBsAg and antibodies to HIV 1 & 2, and HCV was tested serologically.
- During Screening, a Direct Coombs' test was performed on all subjects. Samples were collected at Visits 2 and 3 from all subjects for a Direct Coombs' test and tests for hemolysis (haptoglobin and urine hemosiderin). Subjects with a positive result had a Direct Coombs' test performed on blood drawn before every subsequent IGIV infusion and at all follow-up visits.
- A sample for C-reactive protein.
- Blood was also obtained for 2 additional purposes: (1) Reserve Sample: A 5-mL sample ($\geq$1 mL serum) was obtained before the infusion at each visit, to be stored at -70°C at the central laboratory in the event that repeat tests were required. These samples were discarded at the completion of the study. (2) Retention Sample: To comply with the European CPMP requirements, 4 mL of blood was collected from each subject immediately before the first infusion and at the F1 visit to be sent at the end of the study to --(b)(4)-- in the UK for storage. Serum (1 mL) will be stored in 2-mL tubes at -70°C for 15 years. These samples will be used for serology and NAT testing if required in the future.

Safety Conclusions:
For Study GMX01 The safety profile of Gammaplex was demonstrated by the rate of infusions associated with adverse events during and within 72 hours after infusion being similar to other IGIVs currently in-use (upper 95% confidence limit <0.40). Two serious adverse reactions were reported in one subject during the study: thrombosis and chest pain. However, the safety profile is consistent with that in the labeling of currently licensed IGIV products.

For study GMX03 both Vigam Liquid and Gammaplex had an acceptable safety profile in healthy volunteers. Both were well tolerated at a dose of 400 mg/kg and infusion rates of up to 3 mL/min (Vigam Liquid) and 6 mL/min (Gammaplex) and there was no clinically significant increase in the number or severity of AEs following the higher rate of infusion of Gammaplex up to 6 mL/min in healthy volunteers.

8. Advisory Committee Meeting

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. Other Relevant Regulatory Issues

There were no other regulatory issues raised during the review of this BLA.

10. Labeling

Proprietary Name: The sponsor's proprietary name, GAMMAPLEX, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective during the IND phase and was found to be acceptable with concerns upon initial review on May 7, 2008. However the only finding communicated to the company was the name Gammaplex was accepted. The initial BLA submission review was conducted on May 4, 2008 and the APLB reviewer raised no objections to the Gammaplex name. After additional re-evaluation and consultation with the clinical reviewer, on July 21, 2009, the APLB reviewer re-stated the initial concerns over the Gammaplex name and raised the possibility of requesting the sponsor to submit a new proposed proprietary name for review. These concerns stemmed from (1) the similarity of pronunciation of Gammaplex and another IGIV, Gamunex, may lead to confusion between these two products (2) the presence of the prefix "Gamma" in other IGIV products and (3) the suffix "plex" being present in many other drug names particularly the prothrombin complex concentrates.
On August 17, 2009 the APLB reviewer officially recommended that the proprietary name Gammaplex be found unacceptable. Further discussions between the BLA review committee chairman, the medical reviewer, the head of CRB, the head of the product review branch, and OBRR upper management resulted in OBRR moving to accept the Gammaplex name for the following reasons (1) The names Gammaplex and Gamunex were deemed sufficiently different in spelling and pronunciation to be readily distinguishable with a low likelihood of being confused (2) there are marked differences in the appearance of the vial labels and cartons between the two products (3) the name and the logo for the Gammaplex product has been trademarked and approved for sometime and the rejecting the name this late in the review cycle did not follow the PNR

process as detailed in SOPP 8001.4 (4) accepting Gammaplex is consistent with prior regulatory decisions, as there already a number of approved IGIV names with "Gamma" or "Gam" present in the market and some of these products have almost identical names but different manufacturing processes and/or differences in indications/route of administration (5) in the treatment of PID, the accidental use of one IGIV product over the prescribed IGIV product does not represent a serious health risk.

Physician labeling: The final Gammaplex labeling is PLR compliant.

Full Prescribing Information (FPI): APLB reviewed the original FPI submitted by the applicant. Comments from a promotional and comprehension perspective were provided to OBRR on May 5, 2009. Comments regarding the FPI were conveyed to the applicant on July 16, 2009. The applicant subsequently submitted a revised FPI. APLB reviewed the revised FPI on August 7, 2009 and provided additional comments to OBBR for discussion with the applicant. FDA's comments were conveyed to the applicant on September 1, 2009. The applicant accepted all of FDA's remaining comments and recommendations. All FPI issues have been adequately resolved to proceed with final approved labeling.

Carton and immediate container labels: The carton and container labeling submitted in the original application were reviewed by APLB. Comments on them from a promotional and comprehension perspective were provided on December 11, 2008 (initial comments) and May 5, 2009 (first labeling review). The applicant was informed on December 17 regarding initial carton issues (non-compliance with 21 CFR 610.62) and submitted revised carton and container labeling in March 23, 2009 that APLB reviewed in May 2009. The applicant accepted all outstanding recommendations. All carton/container labeling issues were adequately resolved.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

Except for rejection of the Gammaplex proprietary name by APLB, there were no other review issues requiring resolution, and the review committee recommends the approval of this BLA. The recommendation by APLB reviewer, that the proprietary name be rejected was not implemented as a final determination by the product office and clinical branch after further consideration and consultation with management (as specified in SOPP 8001.4).

b) Risk/ Benefit Assessment

A pharmacovigilance plan has been developed by BPL, and has been reviewed and was found to be acceptable. BPL intends to conduct all postmarketing surveillance by means of routine pharmacovigilance through expedited reporting and addressing the known IGIV class effects in Periodic Safety Update Reports (PSURs). Based on the known risks of the IGIV product class, the proposed programs for post-marketing surveillance appear to be adequate to monitor for adverse outcomes in this patient population.

c) Recommendation for Postmarketing Risk Management Activities
No REMS strategy was implemented as the risk/benefit ratio is well understood for the use of IGIV replacement therapy in PID. The AE/SAE risks IGIV replacement therapy are well established and have been shown be very similar across all IGIV products. No alternate therapies for PID currently exist so there are not risk/benefit ratios for other therapeutic modalities that can be compared to IGIV.

d) Recommendation for Postmarketing Activities

BPL was informed of the following Post-Marketing Requirement:

Your deferred pediatric study required under 505B(a) of the Federal Food, Drug, and Cosmetic Act is required postmarketing study. The status of this postmarketing study must be reported according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below:

1. Deferred pediatric study under PREA for the treatment of primary humoral immunodeficiency in pediatric patients ≥2 to 16 of age: A Phase 3, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of Gammaplex in Primary Immunodeficiency Diseases in Children and Adolescents

   Besides safety and efficacy endpoints, the study design should include pharmacokinetic evaluation in both the children (≥2 to <12 years of age) and adolescent (≥12 to 16 years of age) age groups.

   Protocol Submission: November 2009
   Study Initiation: January 2010
   Study Completion: September 2012
   Final Report Submission: December 2012

Submit final study reports to this BLA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated, "Required Pediatric Assessment."

The following three Post-Marketing Commitments were submitted to the company and agreed to by BPL:

1. --(b)(4)----------

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2. --(b)(4)----------

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3. --(b)(4)---

These PMCs resulted from review of the application and the PAI conducted in May, 2009. There was agreement amongst all the DMPQ and the CMC reviewers that these post-marketing studies were needed and reasonable to request.